Transition metal free intramolecular approach for the synthesis of cyclopenta[b]chromene derivatives from phenol substituted fulvene derived azabicyclic olefins

Ajesh Vijayan a, b, T. V. Baiju a, b, Sunil Varughese c, K. V. Radhakrishnan a, b, *

a Organic Chemistry Section, Chemical Sciences and Technology Division, National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum 695019, India
b Academy of Scientific and Innovative Research (AcSIR), New Delhi 110001, India
c Inorganic Chemistry Section, Chemical Sciences and Technology Division, National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum 695019, India

A facile route towards the synthesis of cyclopentene fused chromene derivatives from strained phenol substituted fulvene derived bicyclic hydrazines is described. The reaction is proceeding through base catalyzed sequential intramolecular ring opening and ring closure of azabicyclic olefins. The transition metal free method provides an easy access to biologically relevant fused chromene ring system under relatively mild reaction conditions.

Chromenes, an important class of heterocycles are structural components in many natural products, pharmaceutical drugs and photosensitive materials.1 The 2H-chromene skeleton containing heterocyclic compounds display anticancer, antioxidant, anti-inflammatory, antitubercular, antiviral, antitumour, antibacterial/antimicrobial, anti-diabetic, anticoagulant, anti-HIV activity.2 Due to the prevalence of these functional moieties in natural products, the development of new methods for their preparation is of significant interest. Different approaches for the synthesis of these important heterocycles by organo/transition metal catalysis have been developed.3 Transition metal catalyzed synthetic approach towards chromene derivatives using palladium,4 copper,5 gold,6 iron7 has been investigated by different research groups. Numerous metal free methods are also developed for the synthesis of chromene core structure using bases like K2CO3,8 DABCO,9 dibenzylamine10 etc. Some of the metal-free intramolecular approach for the synthesis of functionalized 2H-chromenes includes Claisen’s rearrangement of propargyl phenol ethers,11 electrocyclic ring closure of vinylquinone derivatives,12 tetrahydrotetraphosphene catalyzed ylide annulation reaction13 and chiral Bronsted-acid catalyzed allylic alkylation of ortho-allyl alcohol substituted phenol derivatives.14 Even though the catalytic methods developed so far have broad applicability in organic synthesis, further development of novel protocols for the synthesis of fused chromene derivatives is still warranted.

The desymmetrization reactions of diazabicyclic alkenes have been in the limelight of many research groups, and they are one of the best synthons for fabricating a variety of cyclopentene derivatives.15 Transition metal catalyzed ring opening of these diazanorbornene analogues with various organometallic reagents including organoboronic acids,16 organotin compounds,17 organogallium compounds, organoindium compounds18 and aryl iodides19 has been well exploited for the synthesis of biologically significant functionalized cyclopentenes. Our group has developed efficient methods for the synthesis of carbocycles and heterocycles from diazabicyclic olefins via palladium and rhodium catalyzed annulation reactions with various ortho-functionalyzed aryl iodides and salicylaldehydes.20 Furthermore, synthetic transformations of diazabicyclic alkenes through directing group assisted C–H activation of ares furnished highly functionalized cyclopentenes and heterocycle fused azabicycles.21 Micouin et al. reported the palladium catalyzed stereoselective ring opening of diazabicyclic alkenes with soft nucleophiles like phenol for the first time (Scheme 1).22 Our group utilized the same strategy for the ring opening of fulvence derived bicyclic hydrazines and spirotricyclic diazanorbornene analogues.23 Lautens et al. explored the Lewis acid catalyzed intramolecular ring opening of bicyclic hydrazines for the synthesis of aminoazolidinones.24

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Very recently, our group disclosed the Lewis acid catalyzed ring opening of pentafulvene derived diazabicyclic olefins with external nucleophiles such as alcohols, phenols, thiophenols and anilines. Based on the previous reports on desymmetrization of fulvene derived bicyclic hydrazines with external nucleophiles like phenol, we envisaged that installation of a suitable nucleophile at the exocyclic position of pentafulvene will facilitate intramolecular cyclization. In this Letter, we describe our efforts in developing a base catalyzed intramolecular ring opening of phenol substituted fulvene derived bicyclic hydrazines towards the synthesis of highly functionalized cyclopentene fused chromene derivatives.

In order to validate our hypothesis, we commenced our studies with the reaction of salicylaldehyde derived fulvene adduct 1a in the presence of Et3N as base in CH2CN at room temperature for 8 h. The reaction afforded cyclopentene fused chromene derivative 2a in 46% yield (Scheme 2).

The structure of the product 2a was assigned based on various spectroscopic analyses such as 1H NMR, 13C NMR and further confirmation was obtained from HRMS-ESI analysis. The chromene derivative 2a was crystallized from ethyl acetate/hexane mixture, and the stereochemistry was unambiguously confirmed by single crystal X-ray analysis.

To explore the best condition for this reaction, we performed detailed optimization studies with different organic and inorganic bases (Table 1, entries 1–11). Among them, DMAP was found to be the efficient base. Reaction was found to be effective even after adding the base in catalytic amount (Table 1, entry 12). To check the effect of different solvents on the outcome of this organocatalytic transformation, the reaction was carried out in different solvents (Table 1, entries 12–17). The highest yield (66%) for 2a was obtained with CH3CN as the solvent (Table 1, entry 12). After the detailed investigation, the best condition was found to be with 1 equiv of bicyclic hydrazine in the presence of 20 mol % DMAP at room temperature for 8 h furnishing the product 2a in 66% yield.28

Under the optimal conditions various bicyclic olefins derived from different dialkyl azadicarboxylates underwent ring opening followed by intramolecular cyclization and gave the corresponding cyclopentene fused chromene derivatives (2a–2d) in moderate to good yields. The reactivity of bicyclic hydrazines derived from various substituted salicylaldehydes was also explored under similar conditions. Both electron donating and electron withdrawing substituents present on the aromatic ring of fulvene adducts at para-position to the hydroxyl group delivered the fused chromene derivatives in comparable yields. However, further scope of the reaction could not be expanded to substituents at other positions of the aromatic ring due to the instability of the fulvene synthesized. These results are summarized in Table 2.

The mechanism for the reaction can be shown in two different pathways viz. a zwitter ion mechanism (Path I) or an electrocyclic ring closure mechanism (Path II) as illustrated in Scheme 3. Path I commences with the formation of zwitter ion B by the ring opening of pentafulvene derived diazabicyclic olefin due to its inherent instability. Subsequent base induced proton transfer to the hydrazinium ion from the hydroxyl group results in the formation of C. Then the intramolecular attack of phenoxide ion to the allylic cation furnishes cyclopentene fused chromene derivative D. In electrocyclic ring closure mechanism (Path II), the diazabicyclic olefin undergoes a base induced 1,7-hydrogen shift to furnish the intermediate E. Further, the 6π electrocyclic ring closure of E delivers cyclopentene fused chromene derivative D.29

In conclusion, we have unraveled a versatile route for the synthesis of cyclopentene fused chromenes via base catalyzed transformation of phenol substituted fulvene derived diazabicyclic olefins. To the best of our knowledge, this is the first Letter on transition metal free ring opening of pentafulvene derived diazabicyclic alkenes. Investigations on the reactivity of heterobicyclic analogues appended with other nucleophilic moieties towards the synthesis of biologically important molecules are currently underway in our laboratory and will be reported in due course.
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### Supplementary data

Supplementary data (experimental details and characterization data) associated with this article can be found in the online version at [http://dx.doi.org/10.1016/j.tetlet.2016.05.081](http://dx.doi.org/10.1016/j.tetlet.2016.05.081).

### References and notes


26. All the synthesized chromene derivatives bear a hydrazine moiety, and the proton NMR signals of these compounds are broadened due to rotational isomerism exhibited by the hydrazine group. (Ref: Hu, D. X.; Grice, P.; Ley, S. V. *J. Org. Chem.* 2012, 77, 5198). Spectral data for 2a: IR (neat) \( \text{mm}^{-1} \): 3266, 2981, 2928, 2850, 1749, 1692, 1604, 1519, 1480, 1412, 1384, 1310, 1269, 1237, 1130, 1099, 1060, 1000, 858, 758, 664, 608, 555. \( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \): 7.15 (t, \( J = 7.5 \) Hz, 1H), 7.09 (d, \( J = 7.5 \) Hz, 1H), 6.95–6.90 (m, 2H), 6.40–6.13 (m, 4H), 6.02–5.83 (m, 1H), 5.35 (s, 1H), 4.28–4.09 (m, 4H), 1.31–1.20 (m, 6H). \( ^13C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \): 156.2, 153.6, 135.5, 133.2, 129.2, 127.2, 124, 122, 118.2, 117.4, 116.3, 78.8, 63, 62.1, 14.5, 14.3. HRMS (ESI) calcd for C\(_{18}\)H\(_{20}\)N\(_2\)O\(_5\)Na: 367.12699; Found: 367.12756.

27. CCDC 1438504.

28. General procedure for the intramolecular cyclization: The phenol substituted fulvene derived azabicyclic olefin (1 equiv) and base DMAP (20 mol %) were taken in a schlenk tube. The mixture was then dissolved in dry CH\(_3\)CN (2 mL) and allowed to stir at room temperature for 8 h. The solvent was evaporated in vacuo and the residue on silica gel column chromatography using mixtures of EtOAc/hexane yielded cyclopentene fused chromene derivatives in moderate to good yields.
